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# Prasugrel overcomes high on-clopidogrel platelet reactivity in the acute phase of acute coronary syndrome and maintains its antiplatelet potency at 30-day follow-up

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## Abstract

**Background:** *The aim of this study was to assess antiplatelet effect of prasugrel in acute coronary syndrome (ACS) patients with high on-treatment platelet reactivity (HTPR) on clopidogrel, undergoing percutaneous coronary intervention (PCI).*

**Methods:** *A prospective, platelet reactivity-guided, parallel-group, open-label study including 71 patients pretreated with clopidogrel 600 mg and assigned either to prasugrel (30 mg loading dose, 10 mg maintenance dose; n = 46) or clopidogrel (150 mg maintenance dose for 6 days and thereafter 75 mg maintenance dose; n = 25) regimen, based on vasodilator-stimulated phosphoprotein (VASP)-assessed platelet reactivity index (PRI; > 50% vs. ≤ 50%) measured next morning post-PCI.*

**Results:** *Median PRI value after switch to prasugrel sharply declined at 24 h (70.0 [61.3–75.6] vs. 11.9 [6.8–25.7]%; p < 0.000001) and slightly but significantly rose between 24 h and 30 days (27.9 [15.5–46.8]%; p < 0.0006). In contrast, median PRI values in the clopidogrel group were similar at baseline and at 24 h (25.1 [13.7–40.2] vs. 22.0 [18.4–36.8]%; p = NS) and then modestly rose at 30 days (30.3 [20.4–45.7]%; p < 0.03). The prevalence of HTPR decreased in the prasugrel group between baseline and 24 h measurements (100.0 vs. 4.3%; p < 0.0001). Rates of patients with HTPR at 24 h and 30 days were similar in both groups, so were the tendencies in patterns of platelet inhibition evaluated with multiple electrode aggregometry as compared with the VASP assay.*

**Conclusions:** *Our study indicates that prasugrel overcomes HTPR on clopidogrel in the acute phase of interventional treatment of ACS and maintains its antiplatelet potency in 30-day follow-up. Potential clinical benefits of personalized antiplatelet prasugrel-based therapy warrant further investigation in clinical ACS trials. (Cardiol J 2014; 21, 5: 547–556)*

**Key words:** prasugrel, clopidogrel, high on-treatment platelet reactivity, VASP assay, multiple electrode aggregometry

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## Introduction

The modest potency and large interindividual variability of clopidogrel may result in its insufficient antiplatelet effect in some patient subsets [1, 2]. Subsequently, subjects with high on-treatment platelet reactivity (HTPR) on clopidogrel are exposed to increased risk of cardiovascular (CV) events in the setting of percutaneous coronary intervention (PCI) [3].

Prasugrel is associated with a faster onset of action and enhanced inhibition of platelet aggregation than clopidogrel and was shown to reduce CV events more effectively than clopidogrel in patients with acute coronary syndrome (ACS) undergoing PCI [4, 5].

Assuming that a 30 mg loading dose of prasugrel followed by a 10 mg maintenance dose would produce an efficient platelet P2Y<sub>12</sub> receptor blockade in ACS patients treated with PCI and resistant to the initial 600 mg loading dose of clopidogrel, we aimed in the present study to test the antiplatelet effect of prasugrel in interventionally treated ACS patients with HTPR.

## Methods

### Study population and design

The study was designed as a prospective, single-center, non-randomized, investigator-initiated, platelet reactivity-guided, parallel-group, open-label trial. Consecutive patients admitted to The Department of Cardiology and Internal Medicine between 15 November 2010 and 31 December 2011 were screened with respect to their eligibility for the study enrolment. Inclusion criteria were as follows: age between 18 and 74 years, ACS successfully treated with PCI with stent implantation, pre-treatment with loading doses of clopidogrel (600 mg) and aspirin (300 mg), and platelet function assessment available between 12 and 24 h after PCI. Patients were excluded from the study in the presence of at least of one of the following criteria: age equal or above 75 years, prior transient ischemic attack or stroke, body weight less than 60 kg, contraindication for aspirin and/or thienopyridines, the need for anticoagulation in the following month or prior chronic anticoagulation, chronic treatment with a thienopyridine or non-thienopyridine platelet P2Y<sub>12</sub> receptor blocker, necessity for coronary artery bypass grafting in the following month, current bleeding disorder, active bleeding event, active peptic ulcer disease, history of gastrointestinal bleeding within the prior month, severe liver failure (Child Pugh class C), hemoglobin level at

presentation below 90 g/L, platelet count below 100 000/mL and ongoing pregnancy.

Based on the initial platelet function assessment performed on the next morning following PCI, patients were assigned to one of 2 particular thienopyridine regimens (Fig. 1). Blood samples were collected at 10.00 a.m. as we previously demonstrated that platelet inhibition by clopidogrel is weaker in the midmorning hours [6]. Subjects with HTPR on clopidogrel defined as the platelet reactivity index (PRI) above 50% were immediately loaded with 30 mg of prasugrel with a subsequent maintenance dose of 10 mg q.d. until the end of the study. Patients with adequate platelet inhibition (PRI ≤ 50%) received a 150 mg maintenance dose of clopidogrel q.d. for 6 days and thereafter a 75 mg maintenance dose q.d.

All participants provided informed written consents for participation in the study. The study protocol was approved by the Local Ethics Committee in accordance with the Declaration of Helsinki.

### Coronary arteriography and PCI

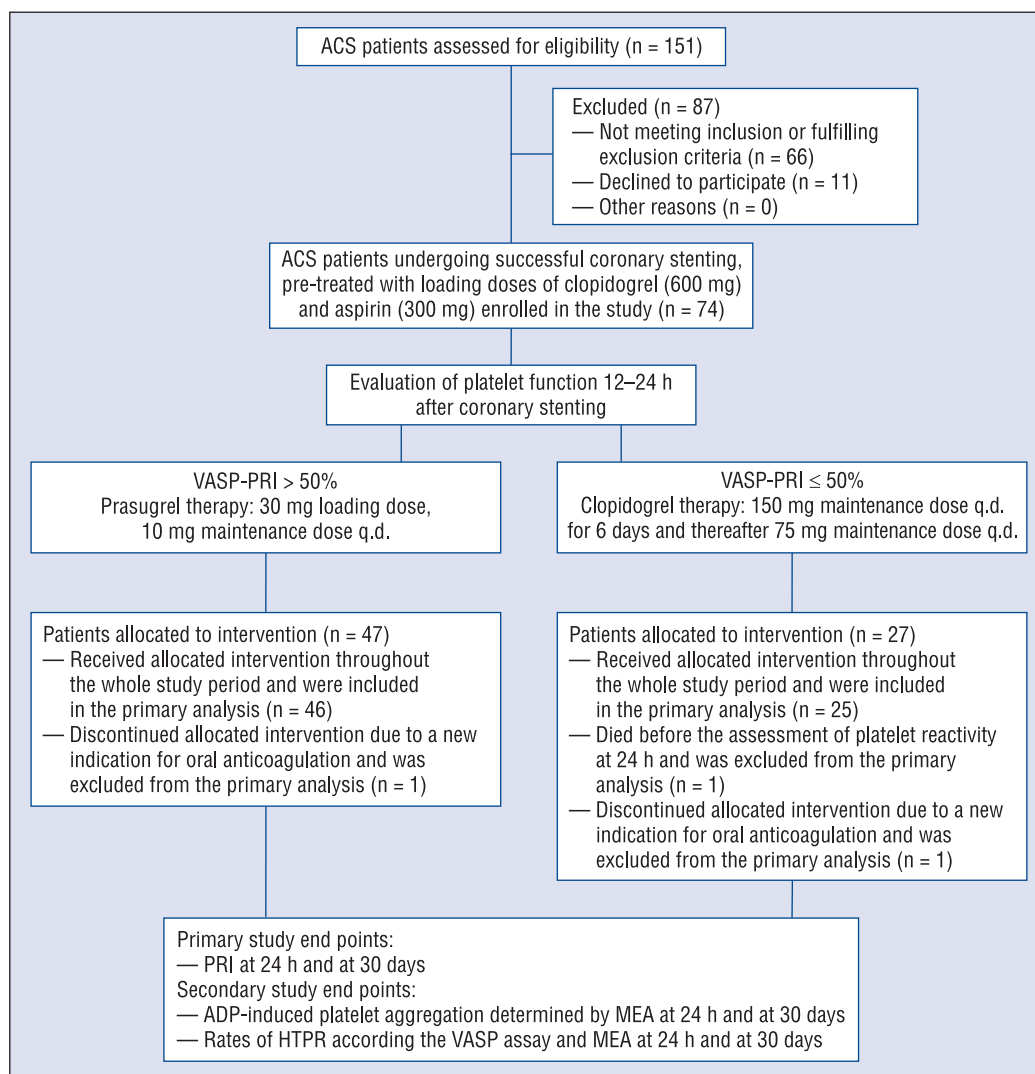
Interventional procedures were performed according to current guidelines [7]. Abciximab or eptifibatide were administered at the discretion of the invasive cardiologist in doses recommended by the drug manufacturers.

### Assessment of platelet reactivity

We applied 2 independent methods to assess platelet reactivity.

A standardized flow cytometric assay (VASP; BioCytex, Marseille, France) was used to determine the inhibition by adenosine diphosphate (ADP) of phosphorylation of vasodilator-stimulated phosphoprotein (VASP), which is mediated by the P2Y<sub>12</sub> receptor through the inhibition of adenylyl cyclase. The VASP assay is regarded as the most specific tool assessing the effect of thienopyridine or non-thienopyridine blockers on the platelet P2Y<sub>12</sub> receptor. Platelet reactivity was expressed as PRI calculated as a percentage according to the formula:  $[(\text{GMFI}_{(\text{PGE1})} - \text{GMFI}_{(\text{PGE1} + \text{ADP})}) / \text{GMFI}_{(\text{PGE1})}] \times 100$ . The ratio is expressed as mean percentage platelet reactivity, inversely correlated with clopidogrel or prasugrel treatment efficiency. The normal value of PRI without treatment with ADP antagonists is 69–100% [8].

Whole blood aggregation was determined using multiple electrode aggregometry (MEA) on a new generation impedance aggregometer (Multiplate Analyzer, Verum Diagnostica GmbH, Munich, Germany) according to the manufacturer's instructions. The instrument detects the impe-



**Figure 1.** Flow diagram of the study; ACS — acute coronary syndrome; ADP — adenosine diphosphate; HTPR — high on-clopidogrel platelet reactivity; MEA — multiple electrode aggregometry; PRI — platelet reactivity index; VASP — vasodilator-stimulated phosphoprotein.

dance change related to platelet aggregation and transforms it into arbitrary aggregation units (AU) that are plotted against time. The area under the aggregation curve (AUC) is an estimator of platelet aggregation that was evaluated in our study. Aggregation, quantified as the AUC, is displayed in arbitrary units ( $10 \text{ AU} \times \text{min} = 1 \text{ U}$ ) [9]. To assess the platelet response to clopidogrel or prasugrel, we applied ADP-induced aggregation. A good reproducibility of MEA, with the variability of results < 6%, was reported by Tóth et al. [9].

### Study definitions and endpoints

The primary HTPR definitions ( $\text{PRI} > 50\%$  and  $\text{AUC} > 46.8 \text{ U}$  for VASP and MEA, respectively)

were based on the consensus document of the Working Group on On-Treatment Platelet Reactivity and prior studies indicating a strong link between increased platelet reactivity and the occurrence of stent thrombosis and recurrent ischemic events [1, 10–15]. To strengthen our findings we also applied in the calculations other clinically validated HTPR definitions ( $\text{PRI} > 60\%$  [16, 17] and  $\text{AUC} > 54 \text{ U}$  [18] for VASP and MEA, respectively).

Values of PRI measured 24 h and 30 days after assignment to the particular thienopyridine regimen constituted the primary study end points, while values of ADP-induced platelet aggregation determined by MEA, rates of HTPR according the VASP assay and MEA, all at 24 h and at 30 days

were selected as the secondary study end points. MEA measurements at baseline and after 24 h were restricted only to the patients not receiving glycoprotein (GP) IIb/IIIa inhibitors. Blood samples for platelet function assessment at 24 h and at 1 month were collected at 10.00 a.m. Additionally, we prespecified to report all cases of death, new onset myocardial infarction, definite stent thrombosis, new onset chronic heart failure and bleeding events of any severity occurring in the study participants during the study period.

### Statistical analysis and sample size calculation

Based on a study conducted by Bonello et al. [14] we assumed the mean value of PRI in HTPR patients pretreated with clopidogrel 600 mg of  $68.5 \pm 10.3\%$ . Similarly, we expected that additional administration of 30 mg of prasugrel in HTPR patients who had received a 600 mg loading dose of clopidogrel would decrease PRI to a value comparable with that observed in clopidogrel-naïve patients after treatment with a 60 mg loading dose of prasugrel ( $34.3 \pm 23.1\%$ ) [19]. Additionally, we anticipated in our prasugrel-treated patients to obtain PRI values at 30 days comparable to these observed in the TRITON-TIMI 38 platelet substudy at this time point ( $33.6 \pm 2.9\%$ ) [20]. Bearing in mind these results and assuming a 2-sided alpha value of 0.05, we calculated, using the t-test for dependent variables, that enrolment of 46 HTPR patients would provide a 99.9% power to demonstrate significant reductions in PRI associated with the implementation of prasugrel-based antiplatelet regimen between its baseline value and both values at 24 h and 30 days.

The Shapiro-Wilk test was used to demonstrate whether the investigated continuous variables were normally distributed. Therefore, continuous variables with and without normal distribution were presented as mean values  $\pm$  standard deviations or as medians and their interquartile ranges, respectively. Depending on the presence or absence of normal distribution, intergroup comparisons were performed with the Student's t-test for independent samples or the Mann-Whitney unpaired rank sum test, whereas the Student's t-test for paired samples or the Wilcoxon matched-paired rank sum test were applied for comparisons within the groups. Independent categorical variables were compared using the  $\chi^2$  test with the Yates' correction if required. Dependent qualitative data were assessed with the McNemar's test. Correlations were tested with the Spearman rank correlation

test. A value of two sided  $p < 0.05$  was regarded as statistically significant;  $0.05 \leq p < 0.1$  was considered a trend towards statistical significance, while  $p \leq 0.1$  was marked as non-significant (NS). The statistical analysis and sample size calculation were carried out using the Statistica 10.0 package (StatSoft, Tulsa, OK, USA) and MedCalc 12.0 (MedCalc Software, Mariakerke, Belgium) statistical software.

## Results

### Study population

A total of 151 individuals were screened with respect to their eligibility for the study and 74 patients were eventually enrolled in the study (Fig. 1). All study participants received allocated antiplatelet regimen. However, 3 patients were excluded from the primary analysis. Finally, 71 patients (46 and 25 patients in the prasugrel and clopidogrel groups, respectively) were included in the primary analysis.

Baseline demographic and clinical characteristics of the study population are provided in Table 1. Similarly, both groups were comparable in terms of angiographic and procedural characteristics. The only discrepancy between both study arms was less common baseline TIMI 3 flow in the prasugrel group (13 [28.3%] vs. 13 [52.0%];  $p < 0.05$ ).

None of the study participants developed new onset myocardial infarction or was diagnosed with definite stent thrombosis at 30-day follow-up. Symptoms of new onset chronic heart failure occurred in 14 (30.4%) patients treated with prasugrel and 8 (32.0%) participants receiving clopidogrel ( $p = \text{NS}$ ). One (2.2%) patient from the prasugrel group reported an increased tendency for bruising. This patient continued therapy with prasugrel throughout the study period. No other bleeding events occurred in our study participants.

### Platelet reactivity

The median time between administration of the 600 mg loading dose of clopidogrel and baseline blood sampling did not differ between the prasugrel and clopidogrel groups (21.0 [14.0–23.5] vs. 20.7 [13.5–23.0] h;  $p = \text{NS}$ ).

Platelet counts evaluated simultaneously with the baseline VASP and MEA measurements were comparable in the overall groups of patients assigned to the prasugrel and clopidogrel regimen (222 [193–258] vs. 243 [198–298]  $\times 10^3 \times \mu\text{L}^{-1}$ ;  $p = \text{NS}$ ), as well as in the subgroups treated without GP IIb/IIIa inhibitors (223 [200–255] vs. 232



**Table 1.** Baseline characteristics of the study population.

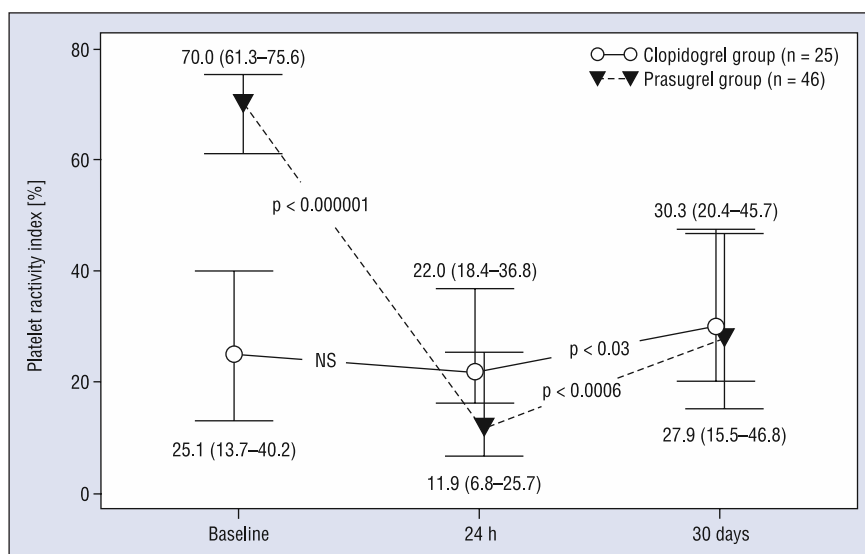
Variable	Prasugrel group (n = 46)	Clopidogrel group (n = 25)	P
Age [years]	58.0 (54.0–65.0)	58.0 (56.0–64.0)	NS
Gender (male/female)	10 (21.7%)/36 (78.3%)	10 (40.0%)/15 (60.0%)	NS
Clinical presentation:			
STEMI	34 (73.9%)	16 (64.0%)	NS
NSTEMI	8 (17.4%)	7 (28.0%)	
Unstable angina	4 (8.7%)	2 (8.0%)	
Anterior location of STEMI	15 (44.1%)	9 (56.2%)	NS
LVEF at discharge [%]	45.0 (40.0–50.0)	45.0 (40.0–50.0)	NS
Prior myocardial infarction	11 (23.9%)	4 (16.0%)	NS
Prior PCI	8 (17.4%)	4 (16.0%)	NS
Prior CABG	2 (4.3%)	2 (8.0%)	NS
Risk factors of coronary artery disease:			
Body mass index [kg/m <sup>2</sup> ]	27.2 (24.0–30.4)	27.4 (25.3–29.9)	NS
Diabetes mellitus	12 (26.1%)	4 (16.0%)	NS
Arterial hypertension	31 (67.4%)	12 (48.0%)	NS
Current smokers	25 (54.4%)	15 (60.0%)	NS
History of smoking	5 (10.9%)	3 (12.0%)	NS
Positive family history	8 (17.4%)	8 (32.0%)	NS
GFR [mL/min/1.73 m <sup>2</sup> ]	93.9 ± 22.5	90.6 ± 17.6	NS
Total cholesterol (mg/dL)	217.8 ± 46.2	221.7 ± 45.4	NS
LDL cholesterol [mg/dL]	150.6 ± 42.0	148.1 ± 38.8	NS
HDL cholesterol [mg/dL]	43.5 (37.0–48.5)	47.0 (37.0–61.0)	NS
Triglycerides [mg/dL]	118.5 (77.0–160.5)	99.0 (75.0–145.0)	NS
Pharmacotherapy during hospitalization:			
Statin use	46 (100.0%)	25 (100.0%)	NS
Beta-blocker use	46 (100.0%)	25 (100.0%)	NS
ACEI use	46 (100.0%)	24 (96.0%)	NS
Proton pump inhibitors use	8 (17.4%)	4 (16.0%)	NS
Calcium-channel blocker use	4 (8.7%)	0 (0.0%)	NS
Glycoprotein IIb/IIIa inhibitor administration	16 (34.8%)	5 (20.0%)	NS

ACEI — angiotensin-converting-enzyme inhibitor; GFR — glomerular filtration rate calculated according to the MDRD equation; CABG — coronary artery bypass grafting; LVEF — left ventricular ejection fraction; NSTEMI — non-ST-segment elevation myocardial infarction; PCI — percutaneous coronary intervention; STEMI — ST-segment elevation myocardial infarction

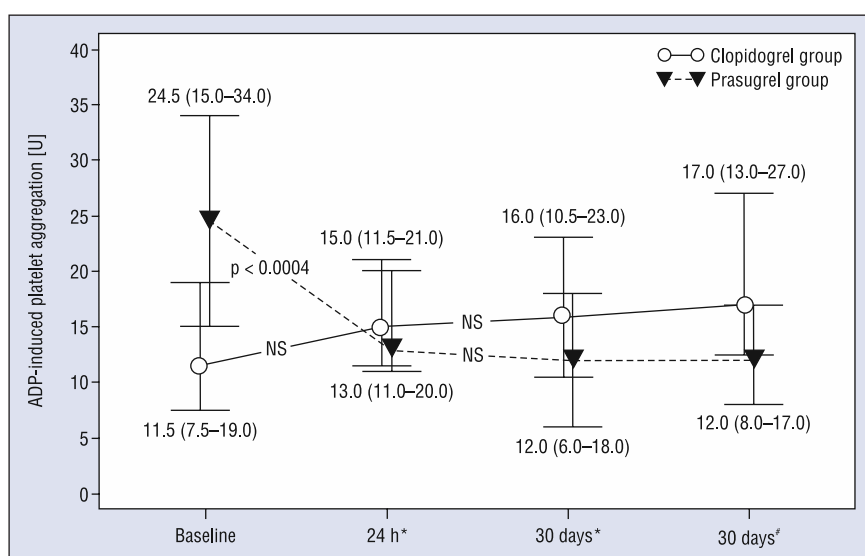
[196–281] × 10<sup>3</sup> × μL<sup>-1</sup>; p = NS). Additionally, we found no significant correlation between both, the baseline PRI and ADP-induced platelet aggregation values, and the platelet count.

The baseline PRI was 60.1 [39.9–71.2]%; 46 (64.8%) and 37 (52.1%) patients after pre-treatment with a 600 mg loading dose of clopidogrel presented with PRI values above the thresholds of 50% and 60% indicating HTPR. Personalized antiplatelet treatment utilized in our study enabled adequate platelet inhibition both at 24 h and at 30 days in the vast majority of our study participants (Figs. 2–5). The prasugrel regimen successfully overcame HTPR on clopidogrel in the acute phase of ACS and maintained its antiplatelet potency in

30-day follow-up while continuation of clopidogrel therapy in patients with an initially appropriate response to a 600 mg loading dose of clopidogrel led to sufficient platelet inhibition in a predominant proportion of patients. In details, the median PRI value after loading with 30 mg of prasugrel sharply declined by 83% at 24 h and slightly, but significantly, rose between 24 h and 30 days (Fig. 2). However, the median PRI value at 30 days in the prasugrel group was merely equal to 40% of its baseline value. In contrast, median PRI values in the clopidogrel group were similar at baseline and at 24 h and then modestly rose at 30 days. As shown in Figure 4, treatment with prasugrel was associated in our study with a significantly lower



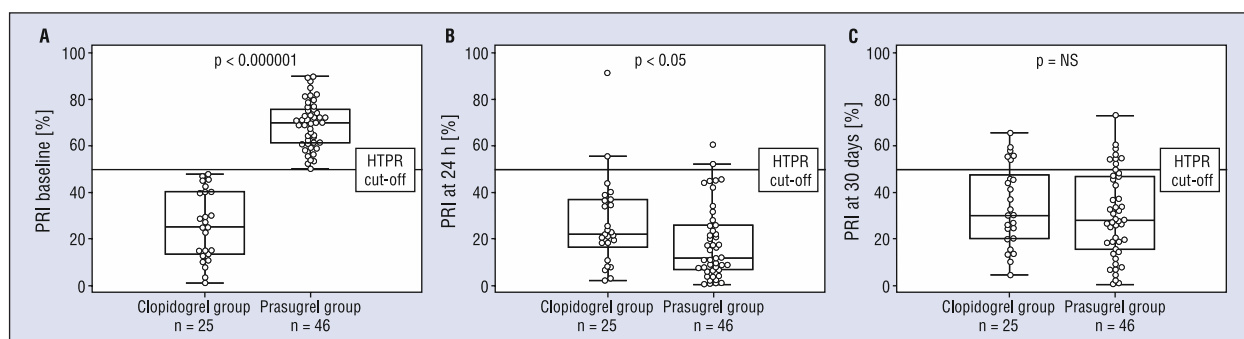
**Figure 2.** Platelet reactivity index according to the antiplatelet regimen. Data are presented as medians and interquartile ranges; p-values refer to differences within the same group between 2 consecutive sampling points.



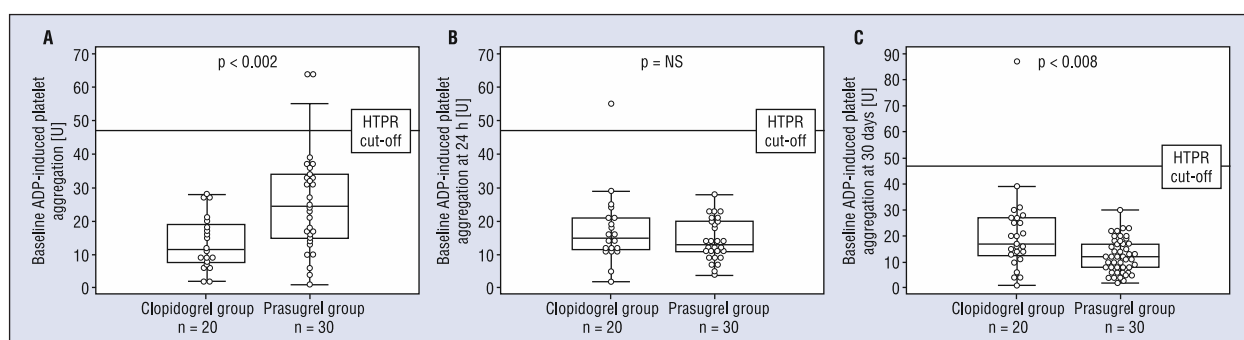
**Figure 3.** Adenosine diphosphate (ADP)-induced platelet aggregation according to the antiplatelet regimen. Data are presented as medians and interquartile ranges; p-values refer to differences within the same group between 2 consecutive sampling points; \* indicates measurements performed exclusively in patients not treated with glycoprotein IIb/IIIa inhibitors (20 and 30 patients in the clopidogrel and prasugrel groups, respectively); # indicates measurements performed in all study participants (25 and 46 patients in the clopidogrel and prasugrel groups, respectively).

median PRI value at 24 h than therapy with clopidogrel. At baseline the numbers of patients with HTPR defined as the PRI value above the cut-offs of 50% and of 60% in the prasugrel and clopidogrel groups were: 46 (100%) vs. 0 (0%) for the cut-off of 50% and 36 (78.3%) vs. 0 (0%) for the cut-off of 60%, at 24 h: 2 (4.3%) vs. 2 (8.0%) for the cut-off of 50% and 1 (2.2%) vs. 1 (4.0%) for the cut-off of

60%, and at 30 days: 8 (17.4%) vs. 6 (24.0%) for the cut-off of 50% and 2 (4.3%) vs. 1 (4.0%) for the cut-off of 60%. Intra- and inter-group comparisons revealed a significant decrease in the proportion of patients treated with prasugrel and diagnosed with HTPR at 24 h when compared to their baseline status (a p-value for both cut-offs  $< 0.0001$ ). All other intra-group comparisons regarding the proportions



**Figure 4.** Individual patient values of platelet reactivity index at various sampling points according to the antiplatelet regimen. Boxes and whiskers represent medians, interquartile ranges and non-outlier ranges; **A**, **B** and **C** refer to measurements performed at baseline, at 24 h and at 1 month, respectively; high on-treatment platelet reactivity (HTPR) cut-off in the figure indicates the threshold of 50%; PRI — platelet reactivity index.



**Figure 5.** Individual patient values of adenosine diphosphate (ADP)-induced platelet aggregation at various sampling points according to the antiplatelet regimen. Boxes and whiskers represent medians, interquartile ranges and non-outlier ranges. **A**, **B** and **C** refer to measurements performed at baseline, at 24 h and at 1 month, respectively; high on-treatment platelet reactivity (HTPR) cut-off in the figure indicates the threshold of 46.8 U.

of patients with HTPR at 2 consecutive sampling points as well as inter-group comparisons of the proportions of patients with HTPR at 24 h and at 30 days indicated the lack of significant differences.

Baseline ADP-induced platelet aggregation assessed exclusively in patients not treated with GP IIb/IIIa inhibitors ( $n = 50$ ) was 17.5 [10.0–31.0] U. Three (6.0%) of these patients after pre-treatment with a 600 mg loading dose of clopidogrel presented with ADP-induced platelet aggregation values above both thresholds of 46.8 U and 54 U, thus indicating HTPR. In general, the pattern of platelet inhibition evaluated with MEA followed tendencies observed with the VASP assay (Fig. 3), both in the prasugrel and clopidogrel groups. The median value of ADP-induced platelet aggregation after loading with 30 mg of prasugrel decreased by 47% at 24 h and remained stable at 30 days. On the other hand, the measurements of ADP-induced platelet aggregation at all 3 sampling points were comparable in the clopidogrel group. As shown in Figure 5, tre-

atment with prasugrel was associated in our study with a significantly lower median value of ADP-induced platelet aggregation at 30 days than therapy with clopidogrel. The baseline numbers of patients with HTPR defined as the ADP-induced platelet aggregation value above the cut-offs of 46.8 U and of 54.0 U in the prasugrel and clopidogrel groups were: 3 (10.0%) vs. 0 (0%) for the cut-off of 46.8 U and 3 (10.0%) vs. 0 (0%) for the cut-off of 54.0 U, at 24 h: 0 (0%) vs. 1 (5.0%) for the cut-off of 46.8 U and 0 (0%) vs. 1 (5.0%) for the cut-off of 54.0 U and at 1 month: 0 (0%) vs. 1 (5.0%) for the cut-off of 46.8 U and 0 (0%) vs. 1 (5.0%) for the cut-off of 54.0 U. Intra-group comparisons regarding the proportions of patients treated either with prasugrel or clopidogrel and presenting with HTPR defined according to any of the applied definitions at 2 consecutive sampling points as well as inter-group comparisons of the proportions of patients with HTPR at any of the sampling points showed no significant differences.



## Discussion

The main finding of our study is that prasugrel overcomes on-clopidogrel HTPR in the acute phase of interventional treatment of ACS and maintains its antiplatelet potency in 30-day follow-up. Platelet inhibition on prasugrel therapy in our study participants with HTPR on clopidogrel was at least as effective as continuation of clopidogrel treatment in patients with an adequate response to a 600 mg loading dose of clopidogrel. Additionally, our results indicate that the 600 mg loading dose of clopidogrel fails to efficiently suppress platelet function in the acute phase of ACS according to the VASP assay in at least one half of patients undergoing PCI.

According to our best knowledge, this is the first study based on the VASP test in conjunction with another platelet function assay, reporting on the ability of prasugrel to overcome on-clopidogrel HTPR in ACS patients. In contrast to most of other trials [21–23], we also investigated the antiplatelet effects of both prasugrel loading and maintenance doses in ACS patients exhibiting HTPR on clopidogrel. Due to the unique property of the VASP assay to reflect selectively the inhibition of the P2Y<sub>12</sub> receptor by antiplatelet agents, the VASP assay in contrast to other methods of platelet function monitoring may be applied in ACS patients treated with GP IIb/IIIa inhibitors. Previous studies on the efficacy of prasugrel in subjects with HTPR on clopidogrel therapy excluded persons receiving GP IIb/IIIa inhibitors and thus investigated highly selected populations [22, 24]. GP IIb/IIIa inhibitors are administered in individuals with unfavorable clinical characteristics including diabetic patients and those with extensive ST elevation myocardial infarction (STEMI), as well as in subjects with a high burden of intracoronary thrombus. These subsets of patients may potentially benefit most from intensified platelet inhibition. Similarly, in our study, patients on adjunctive therapy with GP IIb/IIIa inhibitors when compared with those receiving exclusively aspirin and clopidogrel were numerically more likely to present with HTPR at baseline according to the VASP assay. Not only does the VASP assay facilitate the risk stratification process in ACS patients undergoing PCI [10–14], but according to a recent study, it also provides the best reflection of the *in vivo* plasma level of the active metabolite of clopidogrel when compared with light transmission aggregometry, Verify-Now<sup>®</sup> system, whole blood aggregometry, and the IMPACT-R ADP test [25]. Numerous pharmacodynamic studies including unselected patients in terms of their baseline platelet reactivity demonstrated that pra-

sugrel much stronger than clopidogrel, even with high doses of the latter (i.e. a loading dose of 600 mg and a maintenance dose of 150 mg), inhibits ADP-induced platelet aggregation [20, 26–28]. This intensified platelet inhibition by prasugrel is believed to account for the reduction of ischemic events when compared with clopidogrel therapy in ACS patients undergoing PCI which was shown in the TRITON-TIMI 38 trial [4]. However, recent studies indicated that the phenomenon of HTPR also refers to subjects treated with prasugrel [20, 21]. The prevalence of HTPR defined as the PRI value  $\geq 50\%$  measured 6–12 h after the administration of a 60 mg loading dose of prasugrel among 301 ACS patients successfully treated with PCI in a multicenter French study was 25.2% [19]. This rate corresponds with the prevalence of HTPR on prasugrel at 30 days in the TRITON-TIMI 38 platelet substudy (24% among 51 patients) [20], based on the same definition as applied by Bonello et al. [19].

In the first ever study demonstrating the efficacy of prasugrel in a broad range of post-PCI patients with HTPR on clopidogrel, Alexopoulos et al. [21] showed that prasugrel administered at a single dose of 10 mg per day more effectively inhibited platelet aggregation than clopidogrel at a high dose of 150 mg per day in 64 study participants. However, due to the specific study design (assessment of platelet reactivity at baseline, at 30 days and at 60 days) conclusions regarding the antiplatelet effect of the compared regimens must be restricted to the chronic therapy and cannot be applied to the acute setting when most of cases of stent thrombosis occur. The same research group demonstrated in another randomized study including 60 STEMI patients with HTPR diagnosed with the use of the Verify-Now<sup>®</sup> system 2 h after loading with 600 mg of clopidogrel that prasugrel (60 mg loading dose/10 mg maintenance dose) provides faster and stronger platelet inhibition than a 150 mg maintenance dose of clopidogrel. The authors excluded from the study patients treated with GP IIb/IIIa inhibitors and applied only 1 method of platelet function monitoring. Sardella et al. [23] demonstrated in the randomized, crossover RESET GENE trial, including 32 patients with HTPR on standard clopidogrel regimen who underwent elective coronary stenting, that treatment with a 10 mg maintenance dose of prasugrel was associated with a significantly lower platelet reactivity than a 150 mg maintenance dose of clopidogrel ( $32.6 \pm 10.5$  vs.  $47.9 \pm 20.9$  U according to MEA,  $p = 0.028$ ). No patient treated with prasugrel exhibited HTPR

defined as ADP-induced platelet aggregation with MEA > 45 U, whereas 9 (28.1%) receiving high-dose clopidogrel still had HTPR ( $p = 0.001$ ).

Our results, when combined with the findings of other trials [21–24], provide a solid rationale for the conduction of a carefully designed randomized clinical trial aimed at testing potential clinical benefits of personalized prasugrel-based antiplatelet therapy. In our opinion, such a trial including ACS patients undergoing coronary stenting should compare a non-selective strategy (treatment of all patients with prasugrel) with a selective approach (switching to prasugrel therapy only in patients with HTPR on clopidogrel). We believe that personalized antiplatelet therapy in ACS patients may potentially lead to a reduction of bleeding complications and thus possibly translate into mortality benefits as well as save financial resources and in consequence increase the availability of new platelet P2Y<sub>12</sub> inhibitors in low- and middle-income countries.

### Limitations of the study

Several limitations to our study should be acknowledged. First, our study was performed in a non-randomized fashion. However, we believe that its design allows to prove our study hypothesis convincingly on the ability of prasugrel to overcome HTPR on clopidogrel in ACS patients and to clearly demonstrate that inhibition of platelet function with prasugrel in the setting of HTPR may be at least as effective as the antiplatelet effect of clopidogrel in non-HTPR patients. Furthermore, conduction of a reliable randomized study in the HTPR setting may create substantial difficulties. For example, in the TRIGGER-PCI trial, approximately one third of patients declined randomization when informed that HTPR had been detected [29]. Second, since we only analyzed surrogate end points, the hypothesis that prasugrel improves prognosis in interventional treated ACS patients with HTPR should be verified in adequately powered clinical trials. Third, the limited sample sizes of our study preclude comprehensive sub-group analyses. Fourth, we did not analyze genetic polymorphisms involved in biotransformation of clopidogrel and prasugrel, nor did we assess active metabolites of thienopyridine derivatives [30]. Fifth, although the platelet VASP assay remains a very well validated method of platelet function monitoring, it requires an access to flow cytometry and a skilled technician to be performed.

### Conclusions

Our study indicates that prasugrel overcomes HTPR on clopidogrel in the acute phase of interventional treated ACS and maintains its antiplatelet potency in 30-day follow-up. Potential clinical benefits of personalized antiplatelet therapy based on prasugrel warrant further investigation in clinical trials in the ACS setting.

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